REMARKS/ARGUMENTS

I. Status of the clams

Claim 17 is amended. Claims 27-31 are added, and claims 19-20 are canceled. Claims 1-16 and 22-26 were canceled previously. Thus, claims 17-18, 21, and 27-31 are pending with entry of the amendment.

II. Support for the amendments

Support for the amendments can be found throughout the specification, figures and claims as originally filed. For example, support for claim 1 can be found on, e.g., original claim 1 and paragraph 60 ("modulated levels of the polypeptides of the invention are indicative of insulin resistance"). Support for new claim 27 can be found in, e.g., original claim 1 and paragraph 147. Support for new claims 28-29 can be found in, e.g., paragraph 202. Support for new claim 30 can be found in, e.g., paragraph 118. Support for new claim 31 can be found in, e.g., paragraph 203. No new matter is added.

III. Objection to the specification

The Examiner objected to the presence of a hyperlink in the specification. As amended, the specification no longer includes the hyperlink. Accordingly, withdrawal of the objection is respectfully requested.

IV. Objection to the claims

The Examiner objected to claim 17 as directed to non-elected subject matter. Applicants have deleted the unelected subject matter solely to comply with the Examiner's restriction. Applicants have also canceled claims 19-20 (directed to detection of mRNA), solely to comply with the Examiner's restriction.

As amended, claim 17 omits the language objected to by the Examiner.

Accordingly, withdrawal of the objection is respectfully requested.

V. Rejection under 35 U.S.C. § 112, first paragraph

The Examiner rejected claims 17-18 and 21 as allegedly not enabled for diagnosing Type 2 diabetes. The Examiner relied in part on the Wahab and Murphy references and stated that the "art does not teach if there is a relationship between CTGF levels in lean vs. pre-diabetic or diabetic individuals." *See*, Office Action, page 5. Moreover, the Examiner acknowledged the data in the specification, but argued that specification does not disclose "what level of CTGF in blood or urine ... is indicative of ... Type 2 diabetes or being pre-diabetic." *See*, Office Action, page 6. The Examiner also argued that a large quantity of experimentation would be necessary to establish the relationship of CTGF levels and diabetes or pre-diabetes.

Applicants respectfully traverse the rejection. As amended, the claims are directed to detecting the relative level of insulin resistance in an individual. The present application is the first, to Applicants' knowledge, to present data demonstrating that expression of CTGF is associated with insulin resistance. In particular, the application presents data that shows that:

1. The insulin-sensitizing drug, troglitazone, reduces expression of CTGF in muscle of diabetic people (paragraph 227 and preceding table);

2. Increased levels of CTGF in adipocytes inhibits glucose-transport at all insulin levels tested (paragraphs 228 and 229 and preceding tables);

3. Increased levels of CTGF in L6 myotubes (a model for muscle) inhibits insulin-stimulated glucose transport (paragraph 230 and preceding table).

These data demonstrate for the first time that increased CTGF levels in diabetics function to increase insulin resistance, i.e., the ability of an individual's cells to respond to insulin. In particular, these data show that insulin-stimulated glucose transport (i.e., one of the most recognized downstream cellular responses to insulin) is reduced by when CTGF is expressed. Thus, the data presented in the patent application shows that the level of CTGF is an indicator of insulin resistance. The present patent application therefore taught that "modulated levels of the polypeptides of the invention are indicative of insulin resistance." *See*, the present application, page 16, lines 26-27.

In view of the above-described data, Applicants submit that those of ordinary skill in the art, after reading the present patent application, would have immediately appreciated how to perform the claimed methods to detect CTGF levels from an individual and to correlate those levels to relative insulin resistance. Further, no particular level of CTGF would need to be disclosed in the application to enable those of ordinary skill in the art to determine the relative level of insulin resistance. All that is needed is to compare the level of CTGF in a sample from an individual to a control, wherein a higher level of CTGF in the sample than the control indicates a relatively higher insulin resistance in the individual compared to the control. General methods of correlating protein levels with a disease indication were known as of the filing date of the present application and further detail of performing these methods were provided, e.g., in paragraphs 203-207. In view of the data showing the link of CTGF expression and insulin resistance, undue experimentation was **not** required to practice the claimed methods.

Therefore, Applicants respectfully request withdrawal of the rejection.

VI. Rejections under 35 U.S.C. § 102

A. Wahab et al.

The Examiner rejected claims 17-18 and 21 as allegedly anticipated by Wahab *et al.* Specifically, the Examiner argued that Wahab taught measuring CTGF levels in renal biopsy specimens and also described measuring CTGF in renal tissue from mice having different durations of diabetes. Applicants respectfully traverse the rejection.

The amended claims are directed to a method of detecting the relative level of insulin resistance in an individual. The claims are based on the discovery, first disclosed in the present application, that CTGF expression levels are correlated with insulin-stimulated glucose transport. Thus, CTGF plays a negative role in a cell's ability to respond to insulin. When CTGF expression is high, cells have a higher insulin resistance than when CTGF expression is low. Thus, the present application describes how CTGF mediates signals from insulin and is useful for predicting an individual's predisposition for diabetes, including for testing individuals before they develop diabetes.

In contrast, Wahab speculates on CTGF's role in various symptoms that result once diabetes has occurred. Specifically, Wahab discusses the expression of CTGF in the context of diabetic nephropathy (DN), which is characterized by glomerulosclerosis (scarring of kidney blood vessels, a secondary effect of diabetes). *See*, Wahab, first paragraph, page 77, also last sentence of abstract. Thus, while Wahab *may* comment on some aspects of CTGF's role once diabetes has occurred, Wahab is silent on how insulin and CTGF interact. Indeed, the Examiner acknowledges that "[t]he art does not teach if there is a relationship between CTGF levels in lean vs. pre- diabetic or diabetic individuals." *See*, Office Action, page 5, first full paragraph. Thus Wahab does not teach or suggest a method of detecting the relative level of insulin resistance as recited in the amended claims. Accordingly, Applicants respectfully request withdrawal of the rejection.

B. ***Weitz* et al.**

The Examiner rejected claims 17-18 and 21 as allegedly anticipated by Weitz *et al.* According to the Examiner, Weitz describes:

> a polypeptide 100% identical to SEQ ID NO:2;
>
> the role of CTGF in "overgrowth of connective tissue cells or over-deposition of extracellular matrix and discussed determining the level of the polypeptide ... including [in] diabetic nephropathy....."; and
>
> determining CTGF levels for determining prognosis of a "CTGF-associated disorder" (Office Action, page 10).

Applicants respectfully traverse the rejection. As discussed above, the amended claims are directed to a method of detecting the relative level of insulin resistance in an individual. In contrast, Weitz, like Wahab, focuses on monitoring CTGF as a marker for kidney damage. For instance, the only data provides by Weitz where diabetes is even mentioned is Example 21. Example 21 describes measurement of CTGF in urine of type I diabetics and correlation of kidney damage with CTGF urine levels. *See, e.g.*, Weitz, paragraph 241. Thus, Weitz discusses CTGF as a marker for a secondary effect of diabetes, but does not teach or suggest a relationship between CTGF and insulin signaling or insulin resistance. Thus Weitz

does not teach or suggest a method of detecting the relative level of insulin resistance as recited in the amended claims. Accordingly, Applicants respectfully request withdrawal of the rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

Matthew E. Hinsch
Reg. No. 47,651

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 415-576-0200
Fax: 415-576-0300
Attachments
MEH:meh
61187150 v1